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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,087	03/21/2006	Norikazu Ohtake	BY0031	8948

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,087	OHTAKE ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included cancellation of claims 16-33 and addition claims 34-47, filed on is made of record.

Election/Restrictions

Applicant's election without traverse of Group III, Group III, claims 34-47, drawn to compounds of formula 1 wherein both X^1 and X^2 are CH (i.e. phenyl ring) without traverse in the reply filed on 10/29/2007 is acknowledged.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 3/21/2006, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38-42 are improper dependent claims as they fail to further limit claim 34. The various choices of Y are not fully supported in the choice of Y in claim 34 and hence these claims have broader scope than the claim 34.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 47 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for obesity and diabetes does not reasonably provide enablement for various diseases embraced in the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following apply.

The instant method of use claim 47 is drawn to "method for treating a disease or disorder selected from the group consisting of obesity, diabetes, hormone secretion disorder, hyperlipemia, gout, fatty liver; circulatory system disease, stenocardia, acute cardiac insufficiency, congestive cardiac insufficiency, cardiac infarction, coronary arteriosclerosis, hypertension, nephropathy, sleep disorder, diseases accompanied by sleep disorder, idiopathic hypersomnnia, repetitive hypersomnnia, true hypersomnnia, narcolepsy, sleep periodic acromotion disorder, sleep apnea syndrome, circadian rhythm disorder, chronic fatigue syndrome, REM sleep disorder, senile insomnia, night worker sleep insanitation, idiopathic insomnia, repetitive insomnia, true insomnia, electrolyte metabolism disorder, central nervous system disease, peripheral nervous system disease, bulimia, emotional disorder, melancholia, anxiety, epilepsy, delirium, dementia, schizophrenia, attention deficit/hyperactivity disorder, memory disorder, Alzheimer's disease, Parkinson's disease, sleep disorder, recognition disorder, motion disorder, paresthesia, dysosmia, epilepsy, morphine resistance, narcotic dependency, and alcoholic dependency;".

Instant claim 47, as recited, is a reach through claim. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of histamine H3 receptor activity by the instant compounds, claim 47 reaches through treating various diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of kinase, based on limited assay, it is claimed that treating various diseases such as obesity, diabetes, hormone secretion disorder, hyperlipemia, gout, fatty liver; circulatory system disease, stenocardia, acute cardiac insufficiency, congestive cardiac insufficiency, cardiac infarction, coronary arteriosclerosis, hypertension, nephropathy, sleep disorder, diseases accompanied by sleep disorder, idiopathic hypersomnnia, repetitive hypersomnnia, true hypersomnnia, narcolepsy, sleep periodic acromotion disorder, sleep apnea syndrome, circadian rhythm disorder, chronic fatigue syndrome, REM sleep disorder, senile insomnia, night worker sleep insanitation, idiopathic insomnia, repetitive insomnia, true insomnia, electrolyte metabolism disorder, central nervous system disease, peripheral nervous system disease, bulimia, emotional disorder, melancholia, anxiety, epilepsy, delirium, dementia, schizophrenia, attention deficit/hyperactivity disorder, memory disorder, Alzheimer's disease, Parkinson's disease, sleep disorder, recognition disorder, motion disorder,

paresthesia, dysosmia, epilepsy, morphine resistance, narcotic dependency, and alcoholic dependency in general which is not adequately enabled solely based on the activity of the compounds provided in the specification.

As seen, instant compounds can be used for treating any or all such diseases which is a remarkable finding for which there is no adequate support in the specification.

No compound has ever been found to treat diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine. Although there are various agents acting on histamine receptor in general, they are not being used to treat any or all diseases such as those cited above wherein histamine and its receptor are implicated. Thus, it is beyond the skill of a scientist/clinician today to get a histamine receptor agent to be effective against all diseases generally.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the

inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Bakker R.A., Inflamm. Res. 53, 509-516, 2004, especially the concluding paragraph which states "Based on the modulatory role of the H3 receptor in neurotransmitter release and the high constitutive H3-receptoractivity that is observed in vitro as well as in vivo, inverse H3-receptor agonists will most likely be useful as a potential therapeutic that promotes arousal and attention. Development of H3-receptor isoform-specific ligands may assist future studies that will need to be performed to elucidate the physiological roles of the particular H3-receptor isoforms. Such drugs may also have benefits over general H3-receptor ligands as has been suggested for potential D2-receptor isoform specific drugs. A first step in the development of such potential drugs will be the development of ligands that are selective for the H3 receptor over the H4 receptor". Also Esbenshade et al., molecular intervention, 6, 77-88, 2006, concluding paragraph which says "Despite this complexity, both academic and pharmaceutical laboratories have synthesized a large number of highly potent and selective H3 receptor antagonists, with efficacy in a variety of preclinical animal models of cognition, sleep, and obesity. However, no clinical data for an H3 receptor antagonist are yet available, perhaps reflecting the multiple hurdles related to H3 receptor biology as well as meeting the challenges of producing drug-like molecules. Further understanding of the complex biology of this receptor is clearly mandated, however, given the potential for treating a number of important human diseases".

Both these references suggest the art is still exploratory and that a single agent

may not be able function as a therapeutic agent for treating all the diseases mentioned above.

Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating various diseases that require histamine H3 inhibitory activity.

2) The state of the prior art: Recent publications expressed that the histamine H3 inhibitory activity effects are unpredictable and are still exploratory. See Bakker and Esbenshade et al., cited above especially the concluding paragraph.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating various diseases stated above with the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases

involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating diseases such as obesity, diabetes, hormone secretion disorder, hyperlipemia, gout, fatty liver; circulatory system disease, stenocardia, acute cardiac insufficiency, congestive cardiac insufficiency, cardiac infarction, coronary arteriosclerosis, hypertension, nephropathy, sleep disorder, diseases accompanied by sleep disorder, idiopathic hypersomnnia, repetitive hypersomnnia, true hypersomnnia, narcolepsy, sleep periodic acromotion disorder, sleep apnea syndrome, circadian rhythm disorder, chronic fatigue syndrome, REM sleep disorder, senile insomnia, night worker sleep insanitation, idiopathic insomnia, repetitive insomnia, true insomnia, electrolyte metabolism disorder, central nervous system disease, peripheral nervous system disease, bulimia, emotional disorder, melancholia, anxiety, epilepsy, delirium, dementia, schizophrenia, attention deficit/hyperactivity disorder, memory disorder, Alzheimer's disease, Parkinson's disease, sleep disorder, recognition disorder, motion disorder, paresthesia, dysosmia, epilepsy, morphine resistance, narcotic dependency, and alcoholic dependency and the state of the art is that the effects of kinase inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace large number compounds and large number of diseases related to histamine H3 receptor.

7) The quantity of experimentation needed would be an undue burden to one skilled in

the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 34-37, 45 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Wood et al., WO 00/099388.

See entire document especially see pages 28-29, examples 2 and 3.

Claims 34-37, 45 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohki et al., US 6,107,458.

See entire document especially see column 61 preparation 219.

Claims 34-37, 43 45 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Goel et al., US 3,951,982.

See entire document especially see column 12, entry g and column 13, entry m.

Claims 34-37 and 45-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Apodaca et al., WO 04/37257.

Apodaca et al., teaches several piperidine compounds for treating obesity based on histamine H3 receptor, which include instant compounds. See page 5, formula I and note the definition of variable various groups. Note when L is direct bond, compounds taught by Apodaca et al., include instant compounds. See pages 6-45 for various preferred embodiments and process of making these compounds. See pages 53-86 for examples 1-82. Especially see examples 50-54.

Claims 34-37, 39, 45 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 04/069792.

WO 04/069792 teaches several piperidine compounds for treating pain, which include instant compounds. See page 3, formula I and note the definition of variable various groups. Note when R^4 is a piperidine ring, compounds taught by WO 04/069792 include instant compounds. See pages 4-82 for various preferred embodiments and process of making these compounds. See pages 83-172 for examples 1-274. Especially see page 145, example 183.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-37, 43 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apodaca et al., WO 04/037,257.

Teachings of Apodaca et al., as discussed in the above 102 rejection is incorporated herein. As noted above, Apodaca et al., teaches several piperidine compounds for treating obesity based on histamine H3 receptor, which include instant compounds. See page 5, formula I and note the definition of variable various groups. Note when L is direct bond, compounds taught by Apodaca et al., include instant compounds. See pages 6-45 for various preferred embodiments and process of making these compounds. See pages 53-86 for examples 1-82. Especially see examples 50-54.

Apodaca et al., differs in not exemplifying all compounds of the genus of formula I. But Apodaca et al., teaches equivalency of those compounds exemplified with those generically claimed. Hence, it would be obvious to one trained in the art to make compounds of the genus including instant compounds and expect those compounds have use taught therein in view of equivalency teaching outlined above.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571)

272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624

1/11/2008